UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,208	03/06/2002	Michael C. Pirrung	5405.274	8603

20792 7590 03/22/2004

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
WHISENANT, ETHAN C	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,208	PIRRUNG ET AL.	
	Examiner	Art Unit	
	Ethan Whisenant, Ph.D.	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 JUN 04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-25* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

NON-FINAL ACTION

1. Applicant's election of Group I (**Claims 1-25**) in the paper(s) filed 20 JUN 04 is acknowledged. Claims 26-40 have been cancelled as directed. It is noted that the applicant has not traversed the restriction requirement, distinctly and specifically pointing out any supposed errors in the restriction requirement, therefore, this election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction requirement has been reconsidered, is deemed proper and is therefore, herein made **FINAL**.

SEQUENCE RULES

2. This application complies with the sequence rules and the sequences have been entered by the Scientific and Technical Information Center.

DRAWINGS

3. The drawing(s) filed 06 MAR 02 with this application have been approved by the Examiner under 37 CFR 1.84 or 1.152.

35 USC § 112- 2ND PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

CLAIM REJECTIONS under 35 USC § 112- 2ND PARAGRAPH

5. **Claim(s) 9-11,14 and 23-25** is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 23 are confusing because of the phrase "wherein the detecting said step". Please clarify. Please note that in the prior art rejections which follow the examiner has assumed that this phrase should read "wherein said detecting step".

Claim 14 is indefinite because step (f) lacks proper antecedent basis in Claim 11 and 1. It appears to the examiner that Claim 14 should actually be dependent on Claim 12 and not Claim 11. Please clarify. Please note that in the prior art rejections which follow the examiner has assumed that Claim 14 is dependent on Claim 12 and not Claim 11.

35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claim Rejections under 35 USC § 103

8. **Claim(s) 1-2, and 4-7** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Weng et al. [US 2003/0078736 (24 APR 03)] in view of Pirrung et al. (2001).

Claim 1 is drawn to a method for determining the exons present in a potentially variantly spliced mRNA which method comprises five required steps. To begin, a potentially variantly spliced mRNA is provided, which mRNA is encoded by a DNA which DNA comprises a plurality of exons each of which may or may not be included in said mRNA. Next an array is provided, which array comprises a plurality of different primers immobilized on a solid support at distinct locations thereon, with each of said plurality of different primers selectively hybridizing to a corresponding one of said plurality of exons to form a duplex therebetween; Next the mRNA is contacted with the array so that a duplex is formed between each different primer and each corresponding exon if said corresponding exon is included in said mRNA. Then, the duplexes are subjected to a primer extension reaction such that the primers in said duplexes are extended with at least one labeled base. Finally, the presence or absence of a labeled base on each of said plurality of primers is detected, the presence of said at least one labeled base indicating the presence of the exon to which said primer selectively binds in said potentially variantly spliced mRNA.

Weng et al. teach – see at least for example, paras [0170]-[0176] on pages 15-16 - a method for determining the exons present in a potentially variantly spliced mRNA which comprises all of the limitations of Claim 1 except these authors do not teach subjecting the duplexes formed between a solid phase primer/probe to a primer extension reaction such that the primers in said duplexes are extended with at least one labeled base and then detecting the presence or absence of said labeled primer as an indicator of which exons are present in said in said potentially variantly spliced mRNA. In contrast to the claimed invention Weng et al. teach used flurophore labeled mRNA as the probe (i.e. the species hybridizing to the support).

However, Pirrung et al. do teach a method for solid phase nucleotide primer extension of DNA/ RNA hybrids by Reverse Transcriptase. In addition these authors teach the advantages of their method over standard hybridization analysis like that taught by Weng et al. Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for determining the exons present in a potentially variantly spliced mRNA disclosed by Weng et al. wherein the primer extension methodology is utilized. The motivation to make this modification comes from Pirrung et al. who teach in column 1 on page 2437 the advantages of their

method of detecting hybridization duplexes over that used in the prior art. For example, Pirrung et al. state "Thus, compared to hybridization-based analysis, primer extension methods offer a high signal-to-noise ratio and consequent high fidelity."

Claim 2 is drawn to an embodiment of claim 1, wherein said mRNA comprises mRNA fragments.

Admittedly, Weng et al. do not explicitly teach that their mRNA comprises mRNA fragments. However, this limitation is inherent to the teaching in Weng et al. as all mRNA is composed of (i.e. comprises) mRNA fragments.

Claim 4 is drawn to an embodiment of claim 1, wherein said primer extension reaction is carried out with a reverse transcriptase having a deleted RNase H segment.

Pirrung et al. teach this limitation. It is noted that Pirrung et al. teach utilizing the Tth DNA polymerase, a thermostable RT. See Pirrung et al. Column 2 on page 2439. Tth DNA polymerase is a reverse transcriptase having a deleted RNase H segment. Therefore, it is argued that Pirrung et al. inherently teach this limitation, making the invention of Claim 4 *prima facie* obvious over the combination of Weng et al. in view of Pirrung et al.

Claim 5 is drawn to an embodiment of claim 1, wherein said primers are immobilized to said solid support by the 5' end thereof so that the 3, ends of said primers are available to be extended in said primer extension reaction.

Pirriung et al. teach this limitation. See, at least for example, Figures 1-2 and 4.

Claim 6 is drawn to an embodiment of claim 1, wherein said wherein said mRNA is provided from a biological sample.

Both Weng et al. and Pirriung et al. teach this limitation. See, at least for example, Pirrung et al. Column 2, ¶ 2 on page 2438.

Claim 7 is drawn to an embodiment of claim 1, wherein said mRNA is produced by polymerization from a corresponding cDNA.

Pirriung et al. teach this limitation. See, at least for example, Pirrung et al. Column 2, ¶ 1-2 on page 2438.

9. **Claim(s) 3** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Weng et al. [US 2003/0078736 (24 APR 03)] in view of Pirrung et al. (2001) as applied against Claim 1 above and further in view of Lipshutz et al. [US 5,856,174 (1999)].

Claim 3 is drawn to an embodiment of the method of claim 1, further comprising the step of fragmenting said mRNA prior to said contacting step.

Admittedly, neither Weng et al. or Pirrung et al. explicitly teach fragmenting the mRNA (i.e. the nucleic acid species to be hybridized to oligonucleotide arrays) prior to the contacting step (i.e. prior to the hybridization step). However, as evidenced by Lipshutz et al., it was well known at the time of the invention, to fragment the nucleic acid species to be hybridized to oligo arrays prior to hybridization in order to provide segments which are more readily accessible to the probes, to avoid looping and/or hybridization to multiple probes. See at least for example, Column 8, beginning at line 64 of Lipshutz et al. Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify method for determining the exons present in a potentially variantly spliced mRNA reasonably suggested by the combination of Weng et al. in view of Pirrung et al. wherein the nucleic acid species to be hybridized to oligonucleotide arrays is fragmented prior to the contacting step (i.e. prior to the hybridization step). The motivation to make this modification comes from Lipshutz et al. who teach to fragmenting the nucleic acid species to be hybridized to oligonucleotide arrays prior to hybridization in order to provide segments which are more readily accessible to the arrayed probes, to avoid looping and/or avoid hybridization to multiple probes.

10. **Claim(s) 8** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Weng et al. [US 2003/0078736 (24 APR 03)] in view of Pirrung et al. (2001) as applied against Claim 1 above and further in view of Tarin et al. [US 5,830,646 (1998)].

Claim 8 is drawn to an embodiment of claim 1, wherein said wherein said mRNA is is C44 mRNA.

Admittedly, neither Weng et al. or Pirrung et al. teach detecting C44 mRNA, however, as evidenced by Tarin et al. the C44 mRNA was well known at the time of the invention as was the fact that the C44 mRNA is alternatively spliced.

Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for determining the exons present

in a potentially variantly spliced mRNA reasonably suggested by the combination of Weng et al. in view of Pirrung et al. wherein the potentially variantly spliced mRNA is CD44 mRNA instead of the (ACC) synthetase mRNA taught by Pirrung et al. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

11. **Claim(s) 9-11** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Weng et al. [US 2003/0078736 (24 APR 03)] in view of Pirrung et al. (2001) as applied against Claim 1 above and further in view of Penn et al. [WO0157252 (09 AUG 01)] and Degl'Innocenti et al. (Astract only - 1978).

Claim 9 is drawn to an embodiment of claim 1, wherein said detecting step is followed by two additional required step which steps comprise generating a plurality of values, each of said values indicating the presence or absence of each of said exons in said mRNA; and then generating a code representing the exons present in said mRNA from said plurality of generated values.

Admittedly, neither Weng et al. or Pirrung et al. do not teach the two additional steps recited in Claim 9, however, as evidenced by Penn et al. it was well known at the time of the invention to generate a plurality of values, each of said values indicating the presence or absence of each of said exons in a variantly spliced mRNA. See at least for example, page 95, lines 10-31, Figure 9A-9C, Figure 12 and Claims 31-34. None of Weng et al., Pirrung et al. or Penn et al. teach expressing their results as a code. However, as the use of binary code (a type of digital code) to express the results of an experiment were widely known at the time of the invention as evidenced by Degl'Innocenti et al., it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for determining the exons present in a potentially variantly spliced mRNA reasonably suggested by the combination of Weng et al. in view of Pirrung et al. and Penn et al. wherein the results of the assay are expressed as a binary code. .Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected

functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

12. **Claim(s) 12-14, 16, 18-21** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque et al. [US 2003/0165931 (04 SEP 03)] in view of Pirrung et al. (2001).

Claim 12 is drawn to a method for distinguishing splice variants in a mixed mRNA population which method comprises five required steps. To begin, a mixed mRNA sample is provided, which mRNA sample comprises a plurality of splice variants containing a distinct exon-exon junction not found in each other of said plurality of splice variants. Next an array is provided, which array comprises a plurality of different primers immobilized on a solid support at distinct locations thereon, with each of said plurality of different primers selectively hybridizing to a corresponding one of said plurality of distinct exon-exon junctions to form a duplex therebetween. Next, the mixed mRNA sample is contacted with the array so that a duplex is formed between each different primer and each corresponding splice variant if said corresponding splice variant is included in said mixed mRNA sample. Then, the duplexes are subjected to a primer extension reaction such that the primers in said duplexes are extended with at least one labeled base. Finally, the presence or absence of a labeled base on each of said plurality of primers is detected, wherein the presence of said at least one labeled base indicating the presence of said splice variant in said mixed mRNA sample.

Tocque et al. teach – see at least for example, paras [0174]-[0175] on page 13 - a method for distinguishing splice variants in a mixed mRNA population which comprises all of the limitations of Claim 12 except these authors do not teach subjecting the duplexes formed between a solid phase primer/probe to a primer extension reaction such that the primers in said duplexes are extended with at least one labeled base and then detecting the presence or absence of said labeled primer as an indicator of which splice variant are present in said mixed mRNA sample. In contrast to the claimed invention et al. Tocque et al. teach used flurophore labeled mRNA as the probe (i.e. the species hybridizing to the support).

However, Pirrung et al. do teach a method for solid phase nucleotide primer extension of DNA/ RNA hybrids by Reverse Transcriptase. In addition these authors teach the advantages of their method over standard hybridization analysis like that taught by Tocque et al. Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for distinguishing splice variants in a mixed mRNA population disclosed by Tocque et al. wherein the primer extension methodology is utilized. The motivation to make this modification comes from Pirrung et al. who teach in column 1 on page 2437 the advantages of their method of detecting hybridization duplexes over that used in the prior art. For example, Pirrung et al. state "Thus, compared to hybridization-based analysis, primer extension methods offer a high signal-to-noise ratio and consequent high fidelity."

Claim 13 is drawn to an embodiment of the method of claim 12, wherein said plurality of splice variants comprises at least three. **Claim 14** is drawn to an embodiment of the method of claim 12, wherein said detecting step (e) is followed by step (f) wherein the presence of at least three distinct splice variants is determined from the presence or absence of said labeled base in each of said plurality of primers.

Admittedly, Tocque et al. do not explicitly teach the number of splice variants that can be distinguished. However, absent an unexpected result, it is argued that in view of the teachings present in Tocque et al. any number of splice variants could have been identified.

Claim 16 is drawn to an embodiment of the method of claim 12, wherein said mRNA comprises mRNA fragments.

Admittedly, Tocque et al. do not explicitly teach that their mRNA comprises mRNA fragments. However, this limitation is inherent to the teaching in Tocque et al. as all mRNA is composed of (i.e. comprises) mRNA fragments.

Claim 18 is drawn to an embodiment of the method of claim 12, wherein said primer extension reaction is carried out with a reverse transcriptase having a deleted RNase H segment.

Pirrung et al. teach this limitation wherein these authors teach carrying out a solid phase primer extension reaction with a reverse transcriptase having a deleted RNase H segment. It is noted that Pirrung et al. do teach utilizing the Tth DNA polymerase, a thermostable RT. See Pirrung et al. Column 2 on page 2439. Tth DNA polymerase is a reverse transcriptase having a deleted RNase H segment. Therefore, it is argued that Pirrung et al. inherently teach this limitation, making the invention of Claim 4 *prima facie* obvious over the combination of Tocque et al. in view of Pirrung et al. Also, note that Tocque

et al. teach using a reverse transcriptase devoid of RNase H activity to prepare cDNA, as well as advantages thereof. See Tocque et al. page 3 para [0032].

Claim 19 is drawn to an embodiment of the method of claim 12, wherein said primers are immobilized to said solid support by the 5' end thereof so that the 3, ends of said primers are available to be extended in said primer extension reaction.

Pirriung et al. teach this limitation. See, at least for example, Figures 1-2 and 4.

Claim 20 is drawn to an embodiment of the method of claim 12, wherein said wherein said mRNA is provided from a biological sample.

Both Tocque et al. and Pirriung et al. teach this limitation. See, at least for example, Pirrung et al. Column 2, ¶ 2 on page 2438.

Claim 21 is drawn to an embodiment of claim 12, wherein said mRNA is produced by polymerization from a corresponding cDNA.

Pirriung et al. teach this limitation. See, at least for example, Pirrung et al. Column 2, ¶ 1-2 on page 2438.

13. **Claim(s) 17** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque et al. [US 2003/0165931 (04 SEP 03)] in view of Pirrung et al. (2001) as applied against Claim 1 above and further in view of Lipshutz et al. [US 5,856,174 (1999)].

Claim 17 is drawn to an embodiment of the method of claim 12, further comprising the step of fragmenting said mRNA prior to said contacting step.

Tocque et al. teach fragmenting the nucleic acid species to be hybridized to oligonucleotide arrays prior to the contacting step (i.e. prior to the hybridization step). See at least for example p.29, para[0457]. In addition, as evidenced by Lipshutz et al., it was well known at the time of the invention, to fragment the nucleic acid species to be hybridized to oligo arrays prior to hybridization in order to provide segments which are more readily accessible to the probes, to avoid looping and/or to avoid hybridization to multiple probes. See at least for example, Column 8, beginning at line 64 of Lipshutz et al. Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for distinguishing splice variants in a mixed sample of mRNA reasonably suggested by the combination of Tocque et al. in view of Pirrung et al. wherein the nucleic acid species to be hybridized to oligonucleotide arrays is fragmented prior to the contacting step (i.e. prior to the hybridization step). The motivation to make this modification comes from Lipshutz et al. who teach fragmenting the nucleic acid species to be hybridized to oligonucleotide arrays prior to hybridization in order to provide segments which are more readily accessible to the arrayed probes, to avoid looping and/or to avoid hybridization to multiple probes.

14. **Claim(s) 22** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque et al. [US 2003/0165931 (04 SEP 03)] in view of Pirrung et al. (2001) as applied against Claim 12 above and further in view of Tarin et al. [US 5,830,646 (1998)].

Claim 22 is drawn to an embodiment of claim 12, wherein said wherein said mRNA is is C44 mRNA.

Admittedly, neither Tocque et al. or Pirrung et al. teach detecting C44 mRNA, however, as evidenced by Tarin et al. the C44 mRNA was well known at the time of the invention as was the fact that the C44 mRNA is alternatively spliced.

Therefore, absent an unexpected result, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for distinguishing splice variants in a mixed mRNA population reasonably suggested by the combination of Tocque et al. in view of Pirrung et al. wherein the spliced mRNA is CD44 mRNA instead of the (ACC) synthetase mRNA taught by Pirrung et al. or any of the splice variants disclosed by Tocque et al. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their

expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

15. **Claim(s) 23-25** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque et al. [US 2003/0165931 (04 SEP 03)] in view of Pirrung et al. (2001) as applied against Claim 12 above and further in view of Penn et al. [WO0157252 (09 AUG 01)] and Degl'Innocenti et al. (Astract only - 1978).

Claim 23 is drawn to an embodiment of claim 12, wherein said detecting step is followed by two additional required step which steps comprise generating a plurality of values, each of said values indicating the presence or absence of each of said exons in said mRNA; and then generating a code representing the exons present in said mRNA from said plurality of generated values.

Admittedly, neither Tocque et al. or Pirrung et al. teach the two additional steps recited in Claim 9, however, as evidenced by Penn et al. it was well known at the time of the invention to generate a plurality of values, each of said values indicating the presence or absence of each of said exons in a variantly spliced mRNA. See at least for example, page 95, lines 10-31, Figure 9A-9C, Figure 12 and Claims 31-34. Penn et al. do not teach expressing their results as a code. However, as the use of binary code (i.e. a type of digital code) to express the results of an experiment were widely known at the time of the invention as evidenced by Degl'Innocenti et al., it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method for distinguishing splice variants in a mixed mRNA population reasonably suggested by the combination of Tocque et al. in view of Pirrung et al. and Penn et al. wherein the results of the assay are expressed as a code (i.e. digital code/binary code).

CLAIM OBJECTIONS

16. **Claim(s) 15** is objected to because it is dependent upon a rejected independent base claim.

CONCLUSION

17. **Claim(s) 1-25** is/are rejected and/or objected to for the reason(s) set forth above.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

The fax number for this Examiner is (571) 273-0754. Before faxing any papers please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

ETHAN WHISENANT
PRIMARY EXAMINER

Art Unit 1634

SEARCH NOTES

12 MAR 04

Databases searched: USPATFULL via EAST, EUROPATFULL via EAST, CAplus, Medline

Search terms:

Inventor(s) : e.g. Pirrung M?/au

Array? or microarray?

mRNA and splic$

Splic$ variant?

Primer? or primer? extension

Exon or exon boundry